Medical diagnostic systems

(Orvosbiológiai képalkotó rendszerek)

Elastography

(Elasztográfia)

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Motivation [Konofagou 2004]

- Palpation (stiffness measurement by hand) used for centuries by doctors to detect abnormal tissue
- Example: cancer stiffness >> healthy tissue stiffness
- However, palpation is qualitative and can only detect stiffness changes at skin surface
- For example, breast self-examination often leads to misdiagnosis and is no longer recommended [Baxter *et al.* 2001]

Aim

- method of inducing and measuring displacements *deep* within tissue
- estimate stiffness quantitatively, using a measure such as Young's modulus (E), shear modulus (G), bulk modulus (K), Poisson's ratio (ν)
- avoid image artefacts like speckle

Another motivation: HIFU [Gyöngy 2010]

- High intensity focused ultrasound (HIFU) is a technique to noninvasively destroy tumours by thermal and mechanical means [Kennedy 2005]
- Thermal ablation by HIFU (or indeed ablation by other methods such as RF) causes marked change in stiffness
- Elastography suggested as a method of monitoring HIFU
- In many of the applications mentioned in this lecture, HIFU ablation was used as a method to cause lesions
- This demonstrates the applicability of elastography to monitoring HIFU treatment (though sometimes HIFU creates interference)
- Moreover, HIFU exposure/treatment provides a great "testing platform" for novel elastography methods due to the marked and localised change in stiffness

Overview of this lecture

- Theory
  - viscoelasticity
  - shear and compressional waves
- Applications
  - quasi-static elastography
  - vibration amplitude elastography
  - acoustic radiation force impulse imaging
  - vibroacoustography
  - harmonic motion imaging
  - supersonic shear wave imaging
  - MR elastography
  - pulse wave velocity

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Modelling tissue viscoelasticity

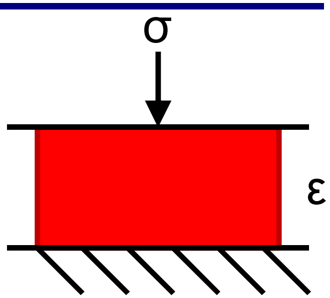
- What happens if tissue is put between two plates and compressed?
- Elastic material (spring model):

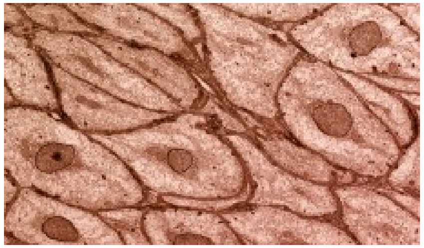
$$\sigma = E\varepsilon$$

- Viscous material (dashpot model):

$$\sigma = \eta(d\varepsilon/dt)$$

- Tissue both elastic and viscous (viscoelastic)
  - Connectin, elastin, cytoskeleton and other fibrils (inside and outside cell) give elasticity
  - Friction of fibers and cells sliding past each other (sometimes increased by cadherin proteins linking them together) provide viscosity [Foty and Steinberg 2005]
- **How do elasticity and viscosity combine?**





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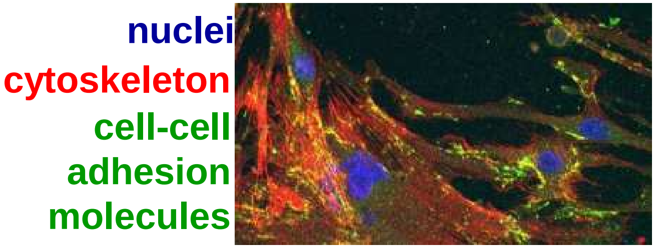

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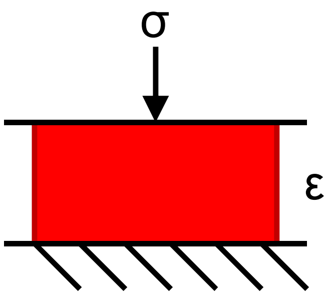
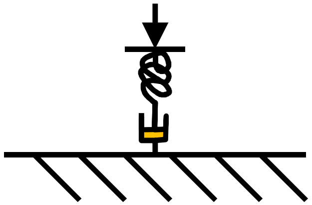
Viscoelastic tissue models

[Gao *et al.* 1996; Hill *et al.* 2004, pp. 100-105]

- Maxwell: tissue keeps shrinking on application of constant stress (creep). Energy dissipation (absorption coefficient α_a) decreases with frequency.
- Voigt: viscous resistance decreases with decreasing velocity, causing exponential shrinkage towards the inviscid case (if stress suddenly released, tissue also *relaxes* in exponential fashion). $\alpha_a \sim f^2$ as $f \rightarrow \infty$
- Time causal: [Szabo 2004, pp. 91-92] dashpot in Voigt replaced by arbitrary response function
- Kelvin/Zener: dashpots in series and parallel with spring. Peak in attenuation for some frequency.
- Multiple relaxation: multiple Kelvin elements cause broad attenuation response with frequency
- Kelvin-Voigt fractional derivative: [Kiss *et al.* 2004] differential operators of fractional powers

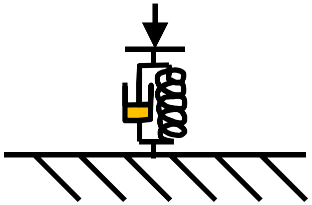


$$\sigma = -\eta/E(d\sigma/dt) + \eta(d\varepsilon/dt)$$



Maxwell model

$$\sigma = E\varepsilon + \eta(d\varepsilon/dt)$$



Voigt model

Viscosity vs. elasticity [Hill *et al.* 2004, pp. 102-103; Kiss *et al.* 2004]

- Strain response to stress due to viscous and elastic elements eqvt. to charge response to voltage in circuit with resistors and capacitors
- Consider Voigt model (eqvt. to resistor and capacitor *in series*):

$$\sigma = E\varepsilon + \eta \mathrm{d}\varepsilon/\mathrm{d}t$$

- Taking Fourier transform:

$$\sigma_F/\varepsilon_F = E(1 + j\omega\tau) \quad \text{(complex elastic modulus)}$$

$$\text{where } \tau = \eta/E \qquad \text{(response or relaxation time)}$$

$\omega = 1/\tau$ is relaxation frequency (*cf.* cutoff frequency in electronics)

- Voigt model does not capture tissue response adequately
- However, it does correctly predict that as frequency is increased strain gets increasingly out of phase with stress, resulting in absorption
- **It also demonstrates that dynamic loading/unloading of tissue can be used to recover not only elasticity, but also viscosity of tissue [Catheline *et al.* 2004]**
- Substitution into wave equation yields $\alpha_a \sim f^2$ [Catheline *et al.* 2004; Raichel 1972] (*cf.* classical [Stokes 1851] thermoviscous formulation [Lighthill 2005; Szabo 1994])

Compression vs. shear

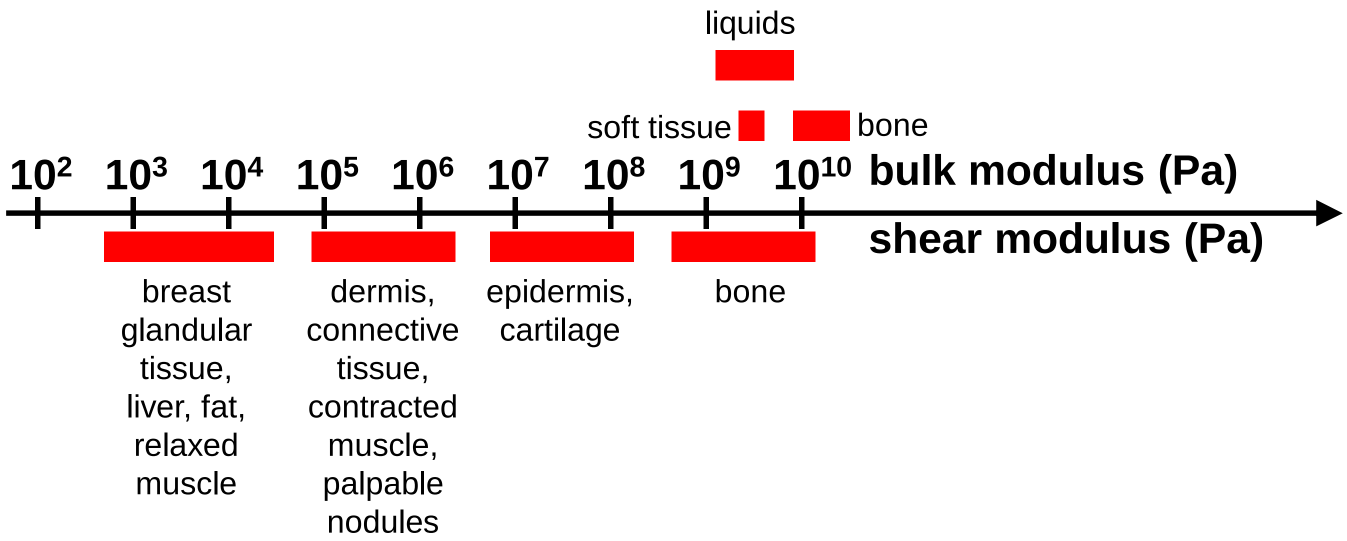
- Both (bulk) compression and shear have elastic and viscous constants
- For tissue, bulk modulus $K \approx 10^4 \times$ shear elastic modulus G
- Hence, since $c_C = \sqrt{(C/\rho)}$, $c_K \approx 10^2 c_G$ (1500 m/s vs. 15 m/s)
- At 1 MHz, this means wavelengths of 1.5 mm vs. 1.5 µm
- Also, at low frequencies (~100 Hz), shear waves dominate, since the low value of G provides a much greater compliance to displacement
- Thus, tissue is relatively incompressible ($\nu \approx 0.5$): $G \approx E/3$ [Parker *et al.* 2005]

(see also http://en.wikipedia.org/wiki/Elastic_moduli for elastic moduli equations)

- Hence, (real component of) elasticity measured by assessing quasi-static or low-frequency displacements is mostly due to shear modulus G
- On the other hand, the shear wave equation is such that the wave amplitude decays by $e^{2\pi}$ (≈535) every wavelength, so that at ultrasonic frequencies shear waves only propagate on the order of micrometers [Cobbold 2007, pp. 86-87]

Shear modulus and waves [Cobbold 2007, pp. 568-571]

- A map of shear modulus *G* provides much higher contrast (and thus differentiation) between different tissues than bulk modulus *K*
- Using external or localised displacements, either measure resulting strain *OR* observe speed of resulting shear wave to infer *G* ($=\rho c_G^2$)
- Thus, promise of quantitative, high contrast and speckle-free images when compared to B-mode imaging (where contrast is due to changes in *K*, ρ)



Comparison of shear and bulk moduli. Adapted from [Sarvazyan *et al.* 1998].

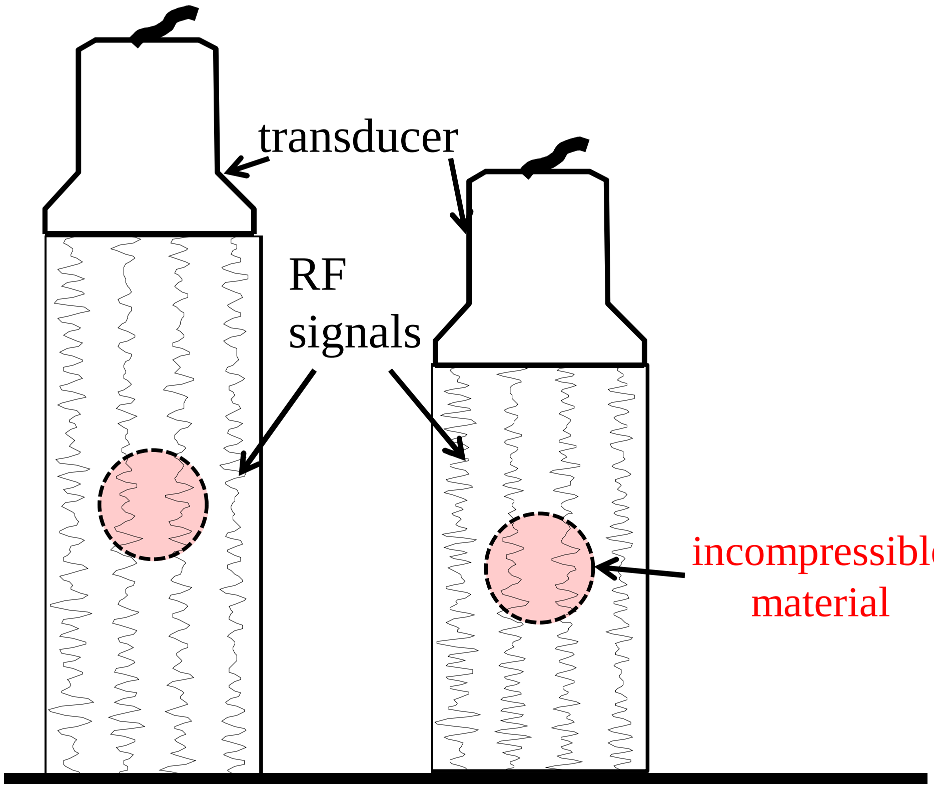
Elastography – approaches [Gao *et al.* 1996; Parker *et al.* 2005]

- Quasi-static compressions (<5 Hz)
  - tissue has time to relax (purely elastic term)
  - variation so slow that wave phenomenon not observable over sample
  - external palpation: free-hand compression with array *OR* mechanical vibrator
  - passive palpation: organ (e.g. motion of lungs or heart)
- Periodic or transient compressions
  - shear waves propagating from boundary such as skin (vibration amplitude elastography) *OR*

    shear waves generated locally in tissue (remote palpation using acoustic radiation force impulse imaging, vibroacoustography, harmonic motion imaging, supersonic shear wave imaging)
  - information about dynamic properties (e.g. viscosity)
- Elastography not exclusively ultrasound technology (MR, PVW)

Quasi-static elastography

- Apply external force
- Estimate localized displacements using cross-correlation methods
- Unknown stress field
- Difficult to obtain quantitative data
- See [Righetti *et al.* 1999] for examples of quasi-static elastograms



Quasi-static elastography schematic. Incompressible red inclusion is detected by taking cross-correlations between A-line segments before and after compression and finding no relative displacement inside inclusion. Figure adapted from [Konofagou 2004].

Vibration amplitude elastography [Gao *et al.* 1996]

- Vibrator placed next to ultrasonic probe generaties shear waves into sample
- Vibration of scatterers causes spectral shifting of the echo
- The spectral shift can be detected using Doppler imaging
- Spectral shift variance proportional to vibration amplitude
- Infer elastic properties from vibration amplitude
- Note also: wavelength of shear wave at e.g. 200 Hz is ~ 5 cm
- Phase and amplitude maps allow visualisation of wave propagation with time
- Gradient of phase and amplitude in direction of wave propagation allow estimates for local shear wave speed and thus shear modulus *G*
- See [Gao *et al.* 1996] for illustrations

Acoustic radiation force impulse (ARFI) imaging

[Fahey *et al.* 2004; Nightingale *et al.* 2001; Nightingale *et al.* 2003]

- Acoustic radiation force (*ARF*) nonlinear phenomenon dependent on attenuation coefficient α, acoustic intensity I and speed of sound c

$$ARF = W_{\text{absorbed}}/c = 2\alpha I/c$$ [Fahey *et al.* 2004]

local strain α local stiffness × local *ARF*

- ~30 μs pulses (pushing beams) focussed at various region of interest
- One pre-ARF pulse-echo; several post-ARF insonation to track temporal response
- Possibility of estimating shear modulus from propagation speed of displacement
- Illustrative example [Fahey *et al.* 2004]:
  - Liver sample injectied with formaldehyde
  - Area around injection expected to stiffen within minutes due to protein cross-linking
  - B-mode: subtle increase in echogenicity observed around affected area
  - ARFI image: affected area shows less displacement due to ARFI, ie tissue has stiffened
  - ARFI image shows much higher contrast

Vibroacoustography [Alizad *et al.* 2006; Alizad *et al.* 2008]

- Similar in principle to ARFI imaging in that localised ARF is generated
- However, here the localised ARF is generated using two overlapping beams of slightly different frequencies (e.g. 3000±15 kHz)
- ARF is ultrasonic: (high-speed) compressional rather than shear waves generated
- Hence, displacement amplitude/propagation cannot be tracked
- Instead, amplitude of emission recorded using hydrophone (receiver matched to water)
- Illustrative example [Alizad *et al.* 2008]:
  - Examining calcifications in an excised human prostate
  - X-ray (traditional method to detect calcifications) and vibro-acoustogram both detect calcifications with excellent contrast
  - Calcification nowhere to be seen on B-mode!

Harmonic motion imaging [Maleke and Konofagou 2008]

- Stems from vibro-acoustography: generate localised harmonic motion
- However, as of late, local vibrations are not induced by two overlapping beams (as in vibro-acoustography), but by amplitude-modulated (AM) ultrasound insonation
- Also, vibration frequency is lower (10–40 Hz) and tracked using cross-correlation of RF A-lines
- More complex than recording with a (cheap) hydrophone, but also potential for more quantitative information
- Viscous component estimated from phase information [Vappou *et al.* 2009]

So far on the remote palpation channel...

... we've been watching the generation of an acoustic radiation force at some location

To provide a map of stiffness over a region of interest

- location of "virtual finger" needed to be scanned (reducing the frame rate) *OR*
- (if applicable) speed of shear wave emanating from pushing location was estimated (shear wave quickly attenuates and several pushing locations were still needed)

Towards supersonic shear imaging – some preliminary observations

- compressional waves much faster than shear waves that they generate
- as a consequence, a pushing location can be set up "instantaneously" compared to the slowness of the shear wave
- what if several pushing beams were generated in quick succession to generate a wavefront?

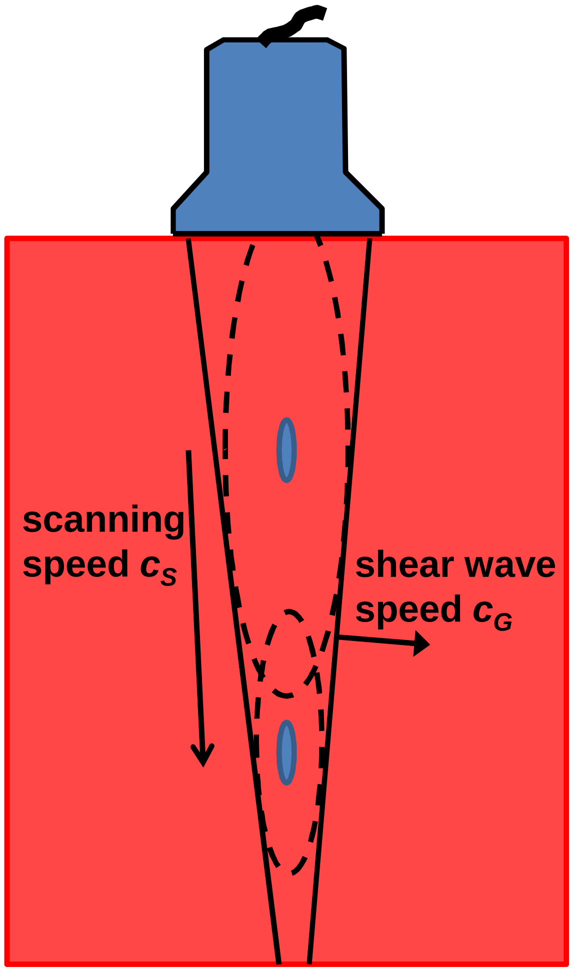
Supersonic shear wave imaging

[Bercoff *et al.* 2004]

- Special case of shear wave velocimetry
- Series of pushing beams synthesised deeper and deeper in tissue, at a scanning speed of c_S
- Wavefront produced propagates at shear wave speed c_G
- E.g. (c_G, c_S) =(2,6) m/s, Mach cone (Mach 3) produced
- Propagation of Mach cone imaged at 3 kHz to provide map of shear modulus

<u>Advantages over ARFI:</u>

- entire plane can be imaged in one fast sequence of pushing beams
- high frame rate of images
- less chance of thermal or mechanical damage to tissue



Adapted from [Bercoff *et al.* 2004].

MR Elastography

- Elastography measures mechanical properties
- Although displacements may be generated by (ultra)sonic transducer, imaging of displacement not limtied to ultrasound!
- Displacements due to static or periodic compressions can be imaged using other modalities (e.g. MR!)

Illustrative example: [Larrat *et al.* 2010]

- MR elastography monitoring experimental HIFU surgery of a restrained rat
- 400 Hz piezoelectric transducer is placed at the head of the rat, generating motion inside the brain
- motion-sensitive gradient (MSG) MR pulse sequence used to measure motion

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Pulse wave velocity (PWV) [Boutouyrie *et al.* 2009; Segers *et al.* 2009]

- Cardiovascular disease is a major health problem worlwide
- Arterial stiffness correlates strongly with cardiovascular health
- As in other forms of wave propagation (e.g. bulk compression, bulk shear), velocity of propagation along vessel is proportional to the square-root of a relevant elastic modulus:

$$PWV = \sqrt{(Eh/\rho D)} \qquad (\sim 10 m/s)$$

(E: Young's modulus; h: wall thickness; ρ: blood density; D: vessel diameter)

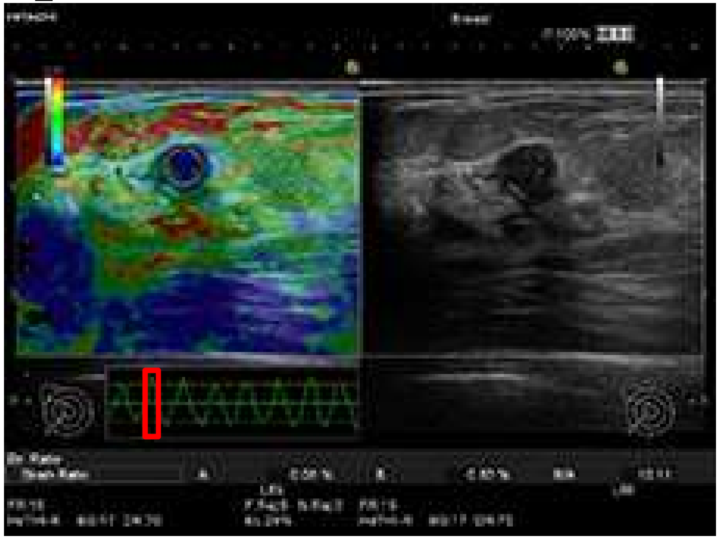
- The wave itself is initiated by the heart during systole and is reflected back to the heart when the wave encounters an arterial branching point
- This reflections allows estimation of the PWV on an ECG (as well as being a source of worry if it returns early due to being an added load on the heart)
- Blood pressure meter, Doppler US, piezoelectric receivers etc. may also be used to estimate PWV

Elastography – commercial implementation

- Increasing number of commercial systems now offer elastography: method gaining acceptance

Example:

- real-time elastography (RTE) of Hitachi Medical Systems
- user applies continuous small (de)compressions with array
- strain graph provides feedback to user of (de)compressions and shows region selected for generation of elastogram



Real-time elastography showing hard circular inclusion. Left: grayscale B-mode with overlaid elastography color map. Right: grayscale B-mode. Bottom left: graph of strain with time, with red box showing region that was used to generate elastogram for maximum SNR. Image courtesy of Hitachi Medical Systems. http://hitachimedicalsystems.com/english/products/us/avius/contents2.html

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